REMARKS/ARGUMENTS:

Claims 1 and 4 are amended. New claims 36-45 are added. Support for the amendment to claim 4 can be found at page 1, lines 24-25 of the Applicant's specification. Support for new claims 36-45 can be found at page 3, lines 13-25 of the Applicant's specification. Claims 1-5 and 36-45 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

Claim Rejections Under 35 U.S.C. § 112:

Claims 1-5 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Applicant respectfully traverses this rejection.

The Examiner states with regard to claim 1 and dependent claims thereof that the term "substantially equivalent" is vague and indefinite. (Office Action, p. 2, §6). The Applicant respectfully disagrees. The specification at page 8, lines 10-11, refers to modifications that can be made in the structure of a peptide that do not "substantially" alter the biological function of the peptide. In making such modifications, substitutions of like amino acid residues can be made on the basis of relative similarity of side-chain substituents, for example, their size, charge, hydrophobicity, hydrophilicity, and the like. (Applicant's specification, at page 8, lines 12-15).

In order to expedite the prosecution of the instant patent application and to more clearly describe the invention, the Applicant has replaced the term "substantially" with "biologically" in claim 1. This amendment does not add new subject matter. Support for the term "biologically equivalent" is found in the specification at page 8, lines 20-22:

> It is understood that an amino acid residue can be substituted for another having a similar hydrophilicity

> value (e.g., within a value of plus or minus 2.0) and still obtain a biologically equivalent polypeptide. (emphasis added)

As discussed above, the specification teaches that it is well known in the art to change the structure of a polypeptide without substantially altering its biological function:

> It is well known in the art that modifications and changes can be made in the structure of a polypeptide without substantially altering the biological function of that peptide. For example, certain amino acids can be substituted for other amino acids in a given polypeptide without any appreciable loss of function. In making such changes, substitutions of like amino acid residues can be made on the basis of relative similarity of side-chain substituents, for example, their size, charge, hydrophobicity, hydrophilicity, and the like. (p. 8, lines 10-15, emphasis added)

The specification teaches maintaining biological equivalence (*i.e.*, anti-angiogenic activity) by substituting an amino acid with another having a similar hydrophilicity value or hydropathicity index. (Specification, p. 8, line 16 - p. 9, line 2) These values are well known and described in the art. The specification teaches that to obtain a biologically equivalent peptide, the substitution should be made using a similar amino acid, *i.e.*, one having a hydrophilicity value or hydropathicity index of within plus or minus 2. Therefore the specification fully defines biological equivalence and claims 1- 5 are not indefinite. Withdrawal of this rejection is thus respectfully requested.

Claims 1-5 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. (Office Action, p. 3, §7) The Applicant respectfully traverses this rejection.

The Examiner states that the term "substantially equivalent" would not allow a skilled artisan to determine what sequences are intended within the scope of the claims. This rejection is moot because "substantially" has been deleted from

claim 1. As discussed above, the specification teaches that a "biologically equivalent" peptide of the amended claims can be made by substituting the amino acids in the peptide with ones that maintain a hydrophilicity value or hydropathicity index of within plus or minus 2. The specification, in the cited passages, provides the hydrophilicity values and hydropathicity indexes (page 8, line 16 – page 9, line 2) of the various amino acids. Based on this teaching and on the fact that it was known in the art how to make substitutions with similar amino acids to obtain biologically equivalent peptides, a skilled artisan would have been able to determine what sequences were intended within the scope of equivalents of SEQ ID NOS: 1 and 2.

Claim 1 has further been amended to limit the peptides based on their anti-angiogenic activity. Support for this limitation is found throughout the specification, *e.g.*, at p. 3, lines 8-16 and lines 22-25, and in the Examples.

In addition to describing biological equivalents of the peptides, the present invention also provides essential structural features that provide the recited function of inhibiting angiogenesis. *E.g.*, in the specification at p. 9, lines 4-6, it is stated that the specific nine-amino-acid region, Pexstatin, found at 582-590 of MMP-2 potently inhibits angiogenesis and tumor growth. Furthermore, Examples 1-4 describe experiments demonstrating that the nine-mer inhibits angiogenesis and tumor growth both *in vitro* and *in vivo*. Example 5 describes the location of Pexstatin within loop-like structures of the hemopexin domain of MMP-2, based on the crystal structure determined for intact MMP-2. Therefore the claimed peptide and its biological equivalents are sufficient for satisfying the written description requirement.

The Examiner also states that the written description provides evidence that the claimed peptides are useful only for the inhibition of angiogenic related disorders and for the treatment of metastasis, but not for the inhibition of any disease. (Office Action, pp. 4-5, § 7) The Applicant respectfully disagrees. However, in order to expedite the prosecution of the instant patent application, the

Applicant has added the limitation "angiogenic" to the term "disease" in claim 4. As explained on page 1, line 24 - page 2, line 10, many diseases (characterized as "angiogenic diseases") are driven by persistent unregulated angiogenesis. This common angiogenic mechanism allows the use of the peptides of the present invention for treatment of various angiogenic diseases.

The specification also provides examples of a number of angiogenic diseases, in which unregulated angiogenesis either causes a particular disease or exacerbates an existing pathological condition (page 1, lines 24-27). Examples of such diseases include, but are not limited to, ocular neovascularization, arthritis, diabetes, and cancer (page 1, line 24 – page 2, line 10). Accordingly, by showing the effect of proteins of the present invention on one class of the angiogenic diseases (cancer), the specification provides necessary written description for the use of the claimed peptides in treatment of all angiogenic diseases. Thus, withdrawal of the failure to comply with the written description requirement rejections under 35 U.S.C. § 112, first paragraph, is respectfully requested.

The Examiner has rejected claims 4-5 under 35 U.S.C. § 112, first paragraph, because "the specification, while being enabling to a peptide of SEQ ID NO: 1 or 2 for the treatment of angiogeneic related cancer and diseases associated with angiogenesis," does not reasonably provide for the treatment of diseases in general, nor does it provide for the broad class of neurological disease. (Office Action, p. 5-7, § 8) This rejection is moot with regard to claim 4 because Applicant has added the limitation "angiogenic" to the term "disease." Claim 5 depends from claim 4 and further limits angiogenic diseases to four specific types. Thus, claim 5 is also enabled by the specification. Withdrawal of this rejection is thus respectfully requested.

Claim Rejection Under 35 U.S.C. § 102:

Claims 1-5 are rejected under 35 U.S.C. § 102(b) as being anticipated by Goldberg GI (WO 98/12309). (Office Action, pp. 7-8, § 10) The Applicant respectfully traverses this rejection.

Amended claim 1 is now limited to a short anti-angiogenic peptide comprising a sequence biologically equivalent to a sequence selected from the group consisting of SEQ ID NO: 1 and SEQ ID NO: 2.

The use of the term "short" peptide in claim 1 is supported by the specification and does not add new subject matter. The specification discloses, at page 3, lines 4-6, that "[s]hort peptides are relatively simple to make and represent a cost effective method of treating disease states in which angiogenesis plays a role and in designing targeted inhibitors of angiogenesis."

A short peptide of the present invention could have a size of 20 amino acids or fewer in length. Peptides of this length are supported by the specification, in that the application specifically discloses the addition of multiple flanking amino acids to a peptide of 9 or 11 amino acids:

> SEQ. ID. NO.: 1—Ile-Phe-Ala-Gly-Asp-Lys-Phe-Trp-Arg
>
> Alternatively, the above sequence may be flanked by other amino acids. For example, the 9 amino acid sequence may be flanked by cysteine residues at the amino and carboxy termini as below:
>
> SEQ. ID. NO.: 2—Cys-Ile-Phe-Ala-Gly-Asp-Lys-Phe-Trp-Arg-Cys
>
> Additionally, the invention provides compositions for inhibiting angiogenesis or tumor growth comprising organic and non-peptidic mimetics based on the above amino acid sequence as well as optimized sequences flanking the region of MMP-2 within which the sequence lies. (p. 3, ll. 17-25, emphasis added)

These passages clearly teach the addition of at least one, and potentially several, flanking amino acids at each terminus of the 9 or 11 amino acid peptides. Therefore, short peptides of 9 or 11 amino acid residues, as in SEQ ID NOS: 1 or 2, additionally including one to five residues at each end and being biologically equivalent are taught by the specification. The Applicant thus believes that short peptides of up to 20 amino acids in length are sufficiently enabled.

With regard to SEQ ID NO: 2, Applicant respectfully submits that Goldberg cannot anticipate present claim 1, because Goldberg does not teach a peptide comprising SEQ ID NO: 2. Goldberg teaches a protein that comprises the nine internal amino acids of SEQ ID NO: 2, but the Goldberg protein lacks both the N-terminal and C-terminal cysteine residues of SEQ ID NO: 2. (Goldberg, page 38, lines 8-9).

With regard to SEQ ID NO: 1, Goldberg teaches a protein of 42 amino acids, whereas amended claim 1 is limited to a "short" peptide. As discussed above, a short peptide would have substantially fewer amino acids than the 42-mer of Goldberg. It is well-known in the art that proteins and large peptides have multiple active sites that bind or interact with other molecules, and it is often not clear whether a particular active site provides the desired therapeutic effect without actually separating the active sites. Often a complex interplay of several active sites is required to achieve the desired biological activity. Moreover, a three-dimensional structure of a peptide is important in establishing a particular physical-chemical environment around an active site and in stimulating covalent and non-covalent interactions between the peptide and its substrate. Thus, not every arbitrary short region of a larger peptide would have the desired anti-angiogenic activity. Additionally, it is often desirable to utilize a shorter peptide to avoid systemic toxicity associated with larger peptides and proteins (page 2, lines 20-24). This objective is met in the short peptides of the present invention.

Goldberg cannot make amended claim 1 obvious. Goldberg does not teach or suggest a short anti-angiogenic peptide comprising SEQ ID NO: 1 or SEQ ID NO: 2.

It is a discovery of the present invention that SEQ ID NOS: 1 and 2 unexpectedly inhibit angiogenesis and tumor growth. (Applicant's specification, at page 3, lines 18-25; page 27, line 4 - page 29, line 9). Goldberg's protein is considerably larger than SEQ ID NOS: 1 or 2. (Goldberg, page 38, lines 1-10) and as acknowledged by the Examiner, it is ***not involved in inhibiting angiogenesis***, metastasis, or a disease.

A person of ordinary skill in the art would not have realized that much smaller peptides, such as short peptides of the present invention, would have the desired biological activity based on the sequence of a larger peptide provided by Goldberg. Looking at the sequence provided by Goldberg, one of ordinary skill in the art could not predict which part of the peptide should be used to preserve its biochemical activity, let alone specifically obtain anti-angiogenic activity. In light of the foregoing, Applicant respectfully submits that Goldberg could not have anticipated or rendered obvious claim 1. Claims 2-5 depend from claim 1 and cannot be anticipated or rendered obvious for at least the same reasons as claim 1. Withdrawal of these rejections is thus respectfully requested.

Claims 1-5 are rejected under 35 U.S.C. § 102(b) as being anticipated by Brooks, P. *et al.* (WO 97/45137). (Office Action, p. 8, § 11) The Applicant respectfully traverses this rejection.

Applicant respectfully submits that Brooks cannot anticipate or render obvious present claim 1, for the same reasons explained with regard to Goldberg, above. Brooks teaches a 222-amino acid protein that comprises the nine amino acids of SEQ ID NO: 1 and the nine internal amino acids of SEQ ID NO: 2 (Brooks, page 1451, lines 23-25). Not only does the Brooks protein lack both the N-terminal and C-terminal cysteine residues of SEQ ID NO: 2, but Brooks teaches a protein of 222 amino acids. As discussed above, amended claim 1 is limited to a "short" peptide. The 222 amino acid protein taught by Brooks would not be expected to have the same biological activity as short peptides of the invention, and might be expected to yield toxicity associated with larger peptides and proteins.

Furthermore, as stated in the Applicant's specification, short peptides are simple and cost effective to make and use for treating disease (page 3, lines 4-6).

Brooks cannot make instant claim 1 obvious. Brooks teaches a 222-amino acid sequence of human MMP-2 (page 64, lines 27-31, SEQ ID NO: 17 on pages 150-151) that has an anti-angiogenic activity (claim 2), and nowhere discloses the use of short peptides. Furthermore, Brooks has no teaching or suggestion of a peptide comprising SEQ ID NO: 2.

In light of the foregoing, Applicant respectfully submits that Brooks does not anticipate or render claim 1 obvious. Claims 2-5 depend from claim 1 and cannot be anticipated or rendered obvious for at least the same reasons as claim 1. Withdrawal of these rejections is thus respectfully requested.

New claims 36-45 are not anticipated nor rendered obvious by Goldberg and Brooks. New claim 36 is limited to a peptide which consists of SEQ ID NO: 1. Similarly, new claim 42 is limited to a peptide which consists of SEQ ID NO: 2. All new claims 36-45 are limited to short peptides. As discussed above, both Goldberg and Brooks teach much larger proteins and peptides that do not anticipate or make obvious short peptides of the present invention.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned attorney at the Los Angeles, California telephone number (213) 337-6700 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
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